

REMARKS/ARGUMENTS

In the Advisory Action dated June 6, 2007, the Examiner indicates that the previously submitted amendments had not been entered. Applicants thank the Examiner for discussing the Advisory Action during a telephone interview on July 19, 2007.

Prior to the present amendments, claims 1, 3-15, 19-21, 23, 26-31, 33 and 36-62 were pending. Claims 1, 2, 4-6, 16-18, 22, 24, 25, 32-41, 43-54 and 62-114 have been cancelled. Claims 3, 7, 9, 11, 13, 15, 19-21, 23, 26-31 and 42 are being amended. After entry of the above amendments, claims 3, 7-15, 19-21, 23, 26-31, 42 and 55-61 will be pending.

Election/Restriction

Claim 1 is being cancelled and claim 42 is being amended with respect to variables R₂, U and V, in accordance with the suggestions made by the Examiner in the final Office Action. The amendments are discussed further below in connection with the rejections under 35 U.S.C. §112, Second Paragraph. Additionally, claims 3, 7, 11, 15, 19-21, 23 and 26-31 are being amended to depend from claim 42 in accordance with the cancellation of claim 1. Please note that the present amendment to claim 42 does not recite that “two R₁₂ are taken together to form a ring,” in accordance with the Examiner’s suggestion in the Advisory Action dated June 6, 2007.

The Examiner indicates that claim 54 does not read on the elected species (see item 3 of the final Office Action and item 1d of the Advisory Action dated April 26, 2007). Applicants maintain that the subject matter of claim 54 is consistent with the elected subject matter, and is readable thereon. However, in order to advance prosecution of the present application, claim 54 is being cancelled.

Rejections under 35 USC §112, Second Paragraph

Claims 1, 3-15, 19-21, 23, 26-31, 33, 36, 42, 43 and 55-61 are rejected as allegedly being indefinite.

In the Advisory Action dated April 26, 2007, the Examiner alleges that the recitation of “ester,” “ketone,” and the like raises new second paragraph issues because those terms refer to

molecules and not moieties (see item 1a of the Advisory Action). Applicants submit that a person skilled in the art would readily understand that monovalent radicals derived from esters, ketones and the like are suitable substituents as used in the claims. However, in order to advance prosecution of the present application, claim 42 has been amended such that the optional substituents listed for U, R₉ and R₁₂ are all monovalent radicals. Accordingly, the rejection of claim 42 as-amended should be withdrawn.

In the Advisory Action dated June 6, 2007, the Examiner alleges that the term “amido” is indefinite. Applicants respectfully disagree. During patent examination, the pending claims **must** be “given their broadest reasonable interpretation consistent with the specification.” MPEP 2111 citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (emphasis added). Indeed, the Examiner has demonstrated that a person skilled in the art would understand that the term “amido” may encompass, for example, C-bound and N-bound species, as well as carboxylic, sulfonic and phosphoric acid species. But, breadth of a claim is **not** to be equated with indefiniteness. MPEP 2173.04 citing *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 USC § 112, second paragraph. Here, the subject matter of the claims is clear since, the term “amido” would be readily understood by those skilled in the art to refer to radicals derived from amides (*i.e.*, radicals of the form –C(=O)-NRR' and/or -NR-C(=O)R', wherein each R and R' are independently hydrogen or a further substituent (*see*, <http://en.wikipedia.org/wiki/Amide>, copy attached)). Still, in an effort to further clarify the scope of the claims, claim 42 is being amended to delete the term “amido” and substitute therefor “monovalent radicals derived from... amides.”

With respect to the terms “oxy” and “carbonyl” as used in claim 42 (see Advisory Action dated June 6, 2007), claim 42 is being amended to remove those terms from the Markush groups and substitute therefore “monovalent radicals derived from aldehydes,... esters and ketones.”

With respect to the phrase “U is a moiety providing 3 atom separation between V and the ring to which R₂ is attached” (see item 5a of the final Office Action and item 1b of the Advisory Action dated April 26, 2007), Applicants thank the Examiner for indicating that the rejection has been overcome by the amendments.

The claims are also rejected because the phrase “V... comprises a basic nitrogen atom that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein” is allegedly indefinite (see item 5b of the final Office Action and item 1b of the Advisory Action dated April 26, 2007). Applicants are amending claim 42 to delete the phrase “that is capable of interacting with a carboxylic acid side chain of an active site residue of a protein,” as suggested by the Examiner. Regarding the comments to claim 7, the Examiner appears to be confusing the definition for “-UV” of claim 7 with the definition for V. V is provided by one of the R₈ groups in claim 7 (and claim 11). Specific embodiments of V are described, for example, in the specification at paragraph [0235]. Independent claim 42 has been amended to incorporate the embodiments of paragraph [0235] for V.

In addition, Applicants are now amending claims 3, 9 13 and 42 to replace the phrase “comprising” with the term “having,” in accordance with the Examiner’s suggestion. Claim 42 is also being amended to replace the phrase “V comprises...” with the phrase “V is selected from the group consisting of...” Accordingly, Applicants respectfully submit that the present amendments are sufficient to completely overcome the second paragraph issue.

In addition, with respect to the phrase “R₃ and R₄ are taken together to form... a 6 membered ring” (see item 5c of the final Office Action and item 1b of the Advisory Action dated April 26, 2007), Applicants maintain that one of ordinary skill in the art would understand the bounds of that phrase as it is used in the present claims. However, the cancellation of claim 1 renders the rejection moot. Applicants thank the Examiner for indicating that the rejection has been overcome by the amendments.

In light of the foregoing, the rejection of claims 1, 3-15, 19-21, 23, 26-31, 33, 36, 42, 43 and 55-61 under 35 USC §112, second paragraph, is believed to be overcome and should be withdrawn.

Miscellaneous Amendments to the Claims

Claim 31 is being amended to delete the redundant phrase “substituted or unsubstituted,” which appears twice in the claim as previously amended.

U.S. Application Serial No. 10/809,636
Advisory Action mailed June 6, 2007
Amendment in Response to Advisory Action Dated July 19, 2007

Patent
DPP4-5004-C1

Double Patenting

The Examiner has provisionally rejected claims 1, 3-15, 19-21, 23, 26-31, 33, 36, 42, 43 and 55-61 under the doctrine of non-statutory obviousness-type double patenting as being unpatentable over claims 1-5, 8, 9, 11-17, 19, 23, 26, 27, 29, 37-39, 51-57, 83, 84, 95, 99 and 111 of copending Application No. 10/809,635 (see item 6 of the final Office Action and item 1c of the Advisory Action dated April 26, 2007). Since the rejection is provisional, Applicants intend to address the rejection when one or both of the applications are otherwise in condition for allowance.

CONCLUSION

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

Dated: July19, 2007

By:



Mitchell R. Brustein
Reg. No. 38,394

Customer No. **32793**
Takeda San Diego, Inc.
10410 Science Center Drive
San Diego, CA 92121
Telephone: (858) 622-8528
Facsimile: (858) 550-0992

Amide

From Wikipedia, the free encyclopedia

In chemistry, an ***amide*** is one of two kinds of compounds:

- the organic functional group characterized by a carbonyl group ($\text{C}=\text{O}$) linked to a nitrogen atom (N), or a compound that contains this functional group (pictured to the right); or
- a particular kind of nitrogen anion.

Amides are the most stable of all the carbonyl functional groups.

Many chemists make a pronunciation distinction between the two, saying (IPA: [ə'mɪd] for the carbonyl-nitrogen compound and ['æmɪd] for the anion. Others substitute one of these pronunciations with ['æmɪd], while still others pronounce both as ['æmɪd], making them homonyms.

In the first sense referred to above, an amide is an amine where one of the nitrogen substituents is an acyl group; it is generally represented by the formula: $\text{R}_1(\text{CO})\text{NR}_2\text{R}_3$, where either or both R_2 and R_3 may be hydrogen. Specifically, an amide can also be regarded as a derivative of a carboxylic acid in which the hydroxyl group has been replaced by an amine or ammonia.

Compounds in which a hydrogen atom on nitrogen from ammonia or an amine is replaced by a metal cation are also known as amides or **azanides**.

The second sense of the word *amide* is the amide anion, which is a deprotonated form of ammonia (NH_3) or an amine. It is generally represented by the formula: $[\text{R}_1\text{NR}_2]^-$, and is an extremely strong base, due to the extreme weakness of ammonia and its analogues as Brønsted acids.

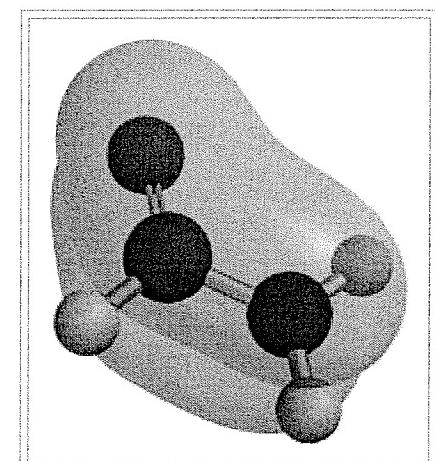
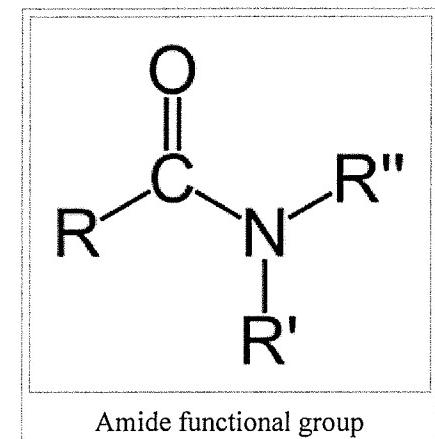
The remainder of this article is about the carbonyl-nitrogen sense of *amide*. For examples of the anionic amide, see the articles Sodium amide and Lithium diisopropylamide.

Contents

- 1 Amide synthesis
- 2 Amide reactions
- 3 Amide linkage (peptide bond)
- 4 Amide properties
- 5 Solubility
- 6 Derivatives
- 7 Naming conventions
- 8 References
- 9 External links

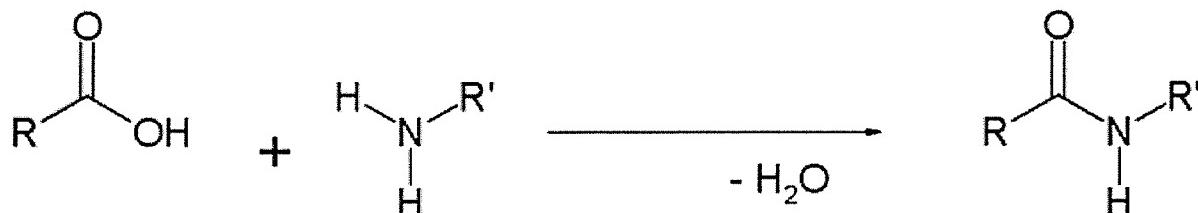
Amide synthesis

- Amides are commonly formed from the reaction of a carboxylic acid with an amine. This is the reaction that forms peptide bonds between amino acids. These amides can participate in hydrogen bonding as hydrogen bond

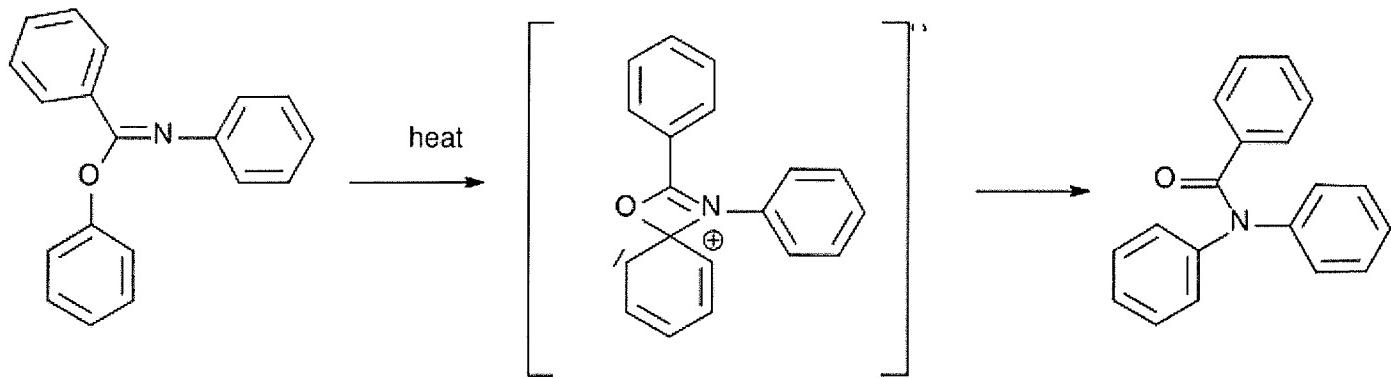


Amides possess a conjugated system spread over the O, C and N atoms, consisting of molecular orbitals occupied by delocalized electrons. One of the π molecular orbitals in formamide is shown above.

acceptors and donors, but do not ionize in aqueous solution, whereas their parent acids and amines are almost completely ionized in solution at neutral pH. Amide formation plays a role in the synthesis of some condensation polymers, such as nylon and Aramid (Twaron / Kevlar). In biochemistry peptides are synthesized in solid phase peptide synthesis. The Schotten-Baumann reaction describes the formation of amides from amines and acid chlorides.



- Cyclic amides are synthesized in the Beckmann rearrangement from oximes.
- Amides also form ketones in the Schmidt reaction
- Amides can be prepared from aryl alkyl ketones, sulfur and morpholine in the Willgerodt-Kindler reaction
- Other amide-forming reactions are the Passerini reaction and the Ugi reaction
- In the **Bodroux reaction** an amide RNHCOR' is synthesized from a carboxylic acid R-COOH and the adduct of a Grignard reagent with an aniline derivative ArNHR' [1] [2]
- In the **Chapman rearrangement** (first reported in 1925) an aryl imino ester is converted to a N,N-diaryl amide:



The reaction mechanism is based on a nucleophilic aromatic substitution. [3]

Amide reactions

- Amide breakdown is possible via amide hydrolysis. Such hydrolysis can occur under basic or acidic conditions. Acidic conditions yield the carboxylic acid and the ammonium ion while basic hydrolysis yield the carboxylate ion and ammonia.
- In the Vilsmeier-Haack reaction an amide is converted into an imine.
- Hofmann rearrangement of primary amides to primary amines.

Owing to their resonance stabilization, amides are relatively unreactive under physiological conditions, even less than similar compounds such as esters. Nevertheless, amides can undergo chemical reactions, usually through an attack of an electronegative atom on the carbonyl carbon, breaking the carbonyl double bond and forming a tetrahedral intermediate. When the functional group attacking the amide is a thiol, hydroxyl or amine, the resulting molecule may be called a cyclol or, more specifically, a thiacyclol, an oxacyclol or an azacyclol, respectively.

The proton of an amide does not dissociate readily under normal conditions; its pK_a is usually well above 15.

However, under extremely acidic conditions, the carbonyl oxygen can become protonated with a pK_a of roughly -1.

Amides will react with nitrous acid (HONO) forming the carboxylic acid and yielding nitrogen. Nitrous acid is formed by addition of a strong acid to a nitrate (III) salt in solution at temperatures of between 0 and 10 degrees.

Amides undergo Hofmann's degradation reaction in which an amide yields an amine with one less carbon atom upon reaction with bromine and sodium hydroxide. One should also note that reacting the amide with the strong reducing agent lithium tetrahydridoaluminate yields an amine with the same number of carbon atoms.

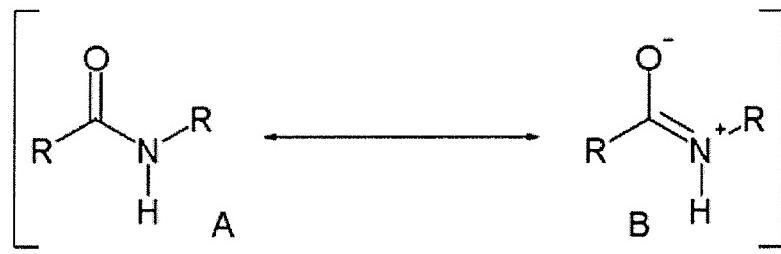
Amides are dehydrated with phosphorus (V) oxide forming the nitrile. Care should be taken when performing such a reaction since phosphorus (V) oxide smoulders when in contact with organic matter.

Amide linkage (peptide bond)

An amide linkage is kinetically stable to hydrolysis. However, it can be hydrolysed in boiling alkali, as well as in strong acidic conditions. Amide linkages in a biochemical context are called peptide linkages. Amide linkages constitute a defining molecular feature of proteins, the secondary structure of which is due in part to the hydrogen bonding abilities of amides.

Amide properties

Compared to amines, amides are very weak bases. While the conjugate acid of an amine has a pK_a of about 9.5, the conjugate acid of an amide has a pK_a around -0.5. Therefore amides don't have as clearly noticeable acid-base properties in water. This lack of basicity is explained by the electron-withdrawing nature of the carbonyl group where the lone pair of electrons on the nitrogen is delocalized by resonance, thus forming a partial double bond with the carbonyl carbon and putting a negative charge on the oxygen. On the other hand, amides are much stronger bases than carboxylic acids, esters, aldehydes, and ketones (conjugated acid pK_a between -6 and -10). It is estimated in silico that acetamide is represented by resonance structure A for 62% and by B for 28% [4]. Resonance is largely prevented in the very strained quinuclidone.



Solubility

Amides contain carbonyl ($\text{C}=\text{O}$) and ether ($\text{N}-\text{C}$) dipoles arising from covalent bonding between electronegative oxygen and nitrogen atoms and electro-neutral carbon atoms. Primary and secondary amides also contain two- and one N-H dipoles, respectively. Because of the pi-bonding arrangement of the carbonyl and the greater electronegativity of oxygen, the carbonyl ($\text{C}=\text{O}$) is a stronger dipole than the N-C dipole. The presence of a $\text{C}=\text{O}$ dipole and, to a lesser extent a N-C dipole, allows amides to act as H-bond acceptors. In primary and secondary amides, the presence of N-H dipoles allows amides to function as H-bond donors as well. Thus amides can participate in hydrogen bonding with water and other protic solvents; the oxygen and nitrogen atoms can accept hydrogen bonds from water and the N-H hydrogen atoms can donate H-bonds. As a result of interactions such as these, the water solubility of amides is greater than that of corresponding hydrocarbons.

While hydrogen bonding may enhance the water solubility of amides relative to hydrocarbons (alkanes, alkenes, alkynes and aromatic compounds), amides typically are regarded as compounds with low water solubility. They are significantly less water soluble than comparable acids or alcohols due to: 1). their non-ionic character 2). the presence

of nonpolar hydrocarbon functionality, and 3). the inability of tertiary amides to donate hydrogen bonds to water (they can only be H-bond acceptors). Thus amides have water solubilities roughly comparable to esters. Typically amides are less soluble than comparable amines and carboxylic acids since these compounds can both donate and accept hydrogen bonds, and can ionize at appropriate pHs to further enhance solubility

Derivatives

Sulfonamides are analogues of amides in which the atom double-bonded to oxygen is sulfur rather than carbon.

Cyclic amides are called lactams.

Naming conventions

- Example: CH_3CONH_2 is named acetamide or ethanamide
- Other examples: propan-1-amide, N,N-dimethylpropanamide, acrylamide
- For more detail see IUPAC nomenclature of organic chemistry - Amines and Amides

References

1. ^ Bodroux F., Bull. Soc. Chim. France, 1905, 33, 831;
2. ^ Bodroux reaction at the Institute of Chemistry, Skopje, Macedonia Link (<http://www.pmf.ukim.edu.mk/PMF/Chemistry/reactions/bodroux1.htm>)
3. ^ *Advanced organic Chemistry, Reactions, mechanisms and structure* 3ed. Jerry March ISBN 0-471-85472-7
4. ^ "Amide Resonance" Correlates with a Breadth of C-N Rotation Barriers Carl R. Kemnitz and Mark J. Loewen J. Am. Chem. Soc.; 2007; 129(9) pp 2521 - 2528; (Article) DOI:10.1021/ja0663024 (<http://dx.doi.org/10.1021/ja0663024>)

External links

- IUPAC Compendium of Chemical Terminology (<http://www.chemsoc.org/chembytes/goldbook/>)

Retrieved from "<http://en.wikipedia.org/wiki/Amide>"

Categories: Amides | Functional groups

-
- This page was last modified 20:29, 4 July 2007.
 - All text is available under the terms of the GNU Free Documentation License. (See **Copyrights** for details.)
Wikipedia® is a registered trademark of the Wikimedia Foundation, Inc., a US-registered 501(c)(3) tax-deductible nonprofit charity.